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A Three-Step Approach Combining Bayesian Regression and NONMEM Population Analysis: Application to Midazolam

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NONMEM, the only available supported program for population pharmacokinetic analysis, does not provide the analyst with individual subject parameter estimates. As a result, the relationship between pharmacokinetic parameters and demographic factors such as age, gender, and body weight cannot be sought by plotting demographic factors vs. kinetic parameters. To overcome this problem, we devised a three-step approach. In step 1, an initial NONMEM analysis provides the population pharmacokinetic parameters without taking into account the demographic factors. Step 2 consists of individual bayesian regressions using the measured drug concentrations for each subject and the population pharmacokinetic parameters obtained in step 1. The bayesian parameter estimates of the individual subject can be plotted against the demographic factors of interest. From the scatter plots, it can be seen which are the demographic factors that appear to affect the pharmacokinetic parameters. In step 3, the NONMEM analysis is resumed, and the demographic factors found in step 2 are entered into the NONMEM regression model in a stepwise manner. This method was used to analyze the pharmacokinetics of midazolam in 64 subjects from 714 plasma concentrations and 11 demographic factors. CL (elimination clearance) and V_1 were found to be a function of body weight. Age and liver disease were found to decrease CL. Of the 11 demographic factors recorded for each patient, none was found to influence V_{ss} or intercompartmental clearance.

KEY WORDS: midazolam kinetics; population analysis.

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INTRODUCTION

Presently, NONMEM is the only available supported program for population pharmacokinetic analysis using a mixed-effect model (5). It enables one to estimate average parameters for the patient population and to assess the influence of demographic factors (the covariates) on these parameters (1). A limitation of NONMEM is that it does not provide the analyst with the parameter estimates for each individual subject. As a result, the analyst cannot directly examine the relationship between demographic factors and pharmacokinetic parameters in a visual manner. The analyst must use an iterative approach to seek for correlations. This approach consists of a sequence of computer runs, in which the analyst builds up, step by step, a model relating demographic factors to pharmacokinetic parameters. In the case that the structural pharmacokinetic model is simple (1) (one-compartment model with two pharmacokinetic parameters, CL and V) and if the number of demographic factors influencing the kinetics is limited (e.g., a data set with only individual body weight and age), the number of possible models to test in the stepwise regression is small. In the simple situation above, one would have to model the influence of age on CL and V and the influence of body weight on CL and V. Since the structure of the relationship between demographic factors and kinetic parameters may have different shapes (linear, exponential, sigmoid, etc.), the total number of computer runs to test all possibilities may approach 20 to 30 in the simple case above.

We have faced the problem of analyzing data from midazolam, a benzodiazepine used in anesthesiology. This drug has an important distribution phase, and an accurate description of its pharmacokinetic behavior necessitates the use of a multicompartment model (2,3). Moreover, our goal was to investigate the possible effect of 11 demographic factors on midazolam kinetics. Under these conditions (4 kinetic parameters, 11 demographic factors), the classical stepwise approach described above would have required hundreds of runs to explore all the possible relationships.

To overcome this problem, we devised a three-step approach integrating bayesian regression with population pharmacokinetic analysis.

METHODS

Patients and Data Collection

A total of 714 midazolam plasma concentrations was obtained from 50 surgical patients at the Kantonsspital Basel (Switzerland) receiving midazolam intravenously for general anesthesia or conscious sedation during regional anesthesia and from 14 volunteers at the Palo Alto Veterans Administration Medical Center (California) receiving midazolam in a study of benzodiazepine pharmacodynamics (total of 64 subjects; average of 9 plasma concentrations available per subject, range of 2 to 26). The following demographic factors were recorded: age (range, 17–89 years), body weight (44–110 kg), chronic alcohol intake (11 subjects drinking more than 20 g alcohol per day), smoking (21 subjects), liver disease (5 subjects: 4 cirrhosis, 1 hepatitis), gender (21 females), concomitant administration of volatile anesthetic agents (17 subjects received halothane, enflurane, or isoflurane), serum creatinine (11 subjects with a serum creatinine between 140 and 1000 μM/l), chronic tranquilizer intake (6 subjects taking benzodiazepines or barbiturates more than twice a week), physical status according to the scale of the American Society of Anesthesiologists (1 = good health; 2 = mild disease; 3 = systemic disease impairing patient activity; 4 = severe disease, life threatening; 5 = dying) (4), and conscious sedation vs. general anesthesia.

Data Analysis

Data analysis was performed using the following three-step approach.

Step 1. In the first step, the computer program NONMEM (version 2, level 1.4) was used to estimate the average pharmacokinetic parameters in the group of patients and volunteers. A two-compartment model, with input and elimination into and from the central compartment, was used in this step (subroutine ADVAN3 from the library of programs provided with the NONMEM-PREDPP package) and the pharmacokinetic parameters estimated by the program were metabolic clearance (CL), intercompartmental clearance (Q), initial volume of distribution (V_1), and volume of distribution at steady state (V_{ss}) (subroutine TRANS3). Interpatient variability was assessed for each pharmacokinetic parameter, according to a proportional error model.

Step 2. This step consists of individual bayesian regression analysis using the measured drug concentrations of each subject and the population parameters obtained in step 1. The bayesian regression was performed with NONMEM (Ref. 5, Vol. II, p. 9). Step 2 provides individual (bayesian) estimates of the pharmacokinetic parameters. By plotting these individual parameter estimates against demographic factors, one can identify which factors correlate with the pharmacokinetic parameters. Moreover, the graphs show the shape of each relationship. These individual bayesian estimates were then plotted against demographic factors, and the resulting graphs examined for relationships.

Step 3. Only the demographic factors showing a correlation with a pharmacokinetic parameter were retained in the analysis. The NONMEM analysis was resumed in the classical way, i.e., the influence of the demographic factors of interest was entered into the pharmacokinetic model sequentially, first for those demographic factors that seemed most correlated with the pharmacokinetic parameters on the graphs, then for those correlations that were less obvious. The shape of the scattergram of parameters vs. demographic factors allowed one to test realistic models. At each step, an additional parameter was estimated by the program, which accounted for the effect size of the demographic factor of interest on a particular pharmacokinetic parameter. The results of this step were compared with those obtained when the influence of the demographic factor in question was not modeled (i.e., no influence was assumed). The following criteria were considered when choosing between the two models: the difference in the −2 log likelihood (LLD) which is supplied by NONMEM (asymptotically χ^2 distributed), the standard error and correlation matrix of the parameter estimates, the plots of the residuals, and the change in the remaining interindividual variability in the pharmacokinetic parameters. A $P < 0.005$ (corresponding to a LLD of 7.8) was chosen to decide whether a covariate should be included in the model. This P value is conservative, because of the asymptotic nature of the χ^2 test. Once an important covariate was identified, it was left in the model, and other covariates were tested in turn against this new model. Finally, the random effects (the inter- and intraindividual variability components) were evaluated with the best model found for the fixed effects (pharmacokinetic parameters and covariates). A proportional error model was used for both inter- and intraindividual variability. Additionally, after the final model was found, each covariate was in turn deleted from the full model, and the reduced model was tested against the full model, as a final check.

RESULTS

The results of step 1 are shown in Table I. The table provides estimates of population kinetic parameters for midazolam without taking into account any demographic factors.

From the 64 bayesian regressions performed in step 2, individual pharmacokinetic parameter sets were obtained and plotted against the demographic factors (4 pharmacokinetic parameters × 11 demographic factors = 44 scatter plots). The scatter plots with the most profound demographic effect are presented in Fig. 1 (correlation between body weight and CL), in Fig. 2 (correlation between body weight and V_1), and in Fig. 3 (inverse correlation between age and CL). Liver disease was also shown to be associated with a smaller clearance. No correlation was found between body weight and V_{ss}.

Table I. Step 1 Results: Global NONMEM Estimates of Midazolam Pharmacokinetic Parameters[a]

	Parameter estimate	SE	Interindividual variability (CV)
CL	300 ml · min^{-1}	40	+71%/−42%
V_1	30.3 L	1.7	+32%/−24%
Q	590 ml · min^{-1}	100	+59%/−37%
V_{ss}	14.4 L	9.2	+92%/−48%
Residual intraindividual variability: ±18%			
−2 • log likelihood value: 4462			

[a]SE, standard error of estimates; CV, coefficient of variation.

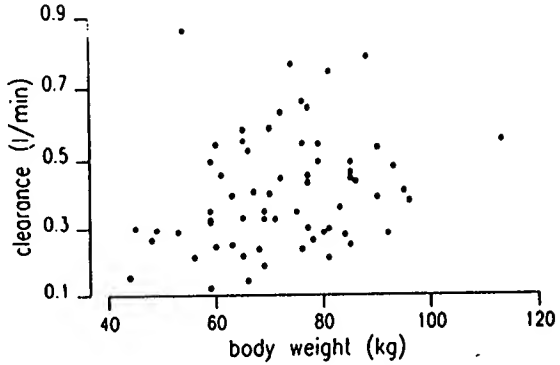

Fig. 1. Scatter plot of individual clearances (bayesian estimates) vs. body weight.

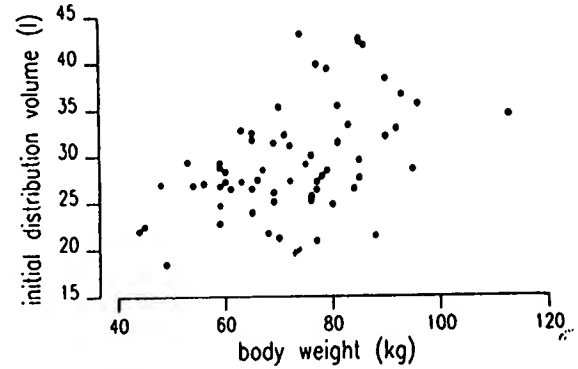

Fig. 2. Scatter plot of individual V_1 (bayesian estimates) vs. body weight.

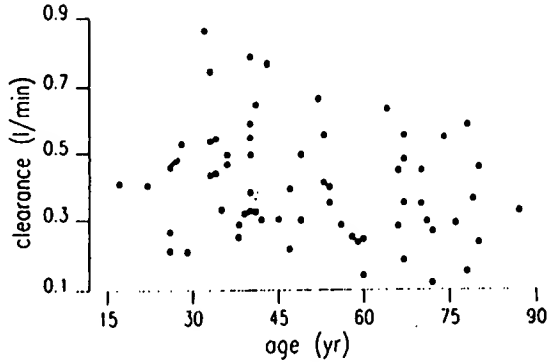

Fig. 3. Scatter plot of individual clearances (bayesian estimates) vs. age.

In step 3, the effect of age, body weight, and liver disease were sequentially entered into the NONMEM model. The final results are shown in Table II.

DISCUSSION

Graphic display helps visualizing the correlation between demographic factors and pharmacokinetic parameters. The proposed method uses

Table II. Final Results[a]

Final model for CL			
$CL = BW \cdot (\Theta_{CL} - F_{age}) \cdot F_{liver}$			
If age > 40 years then $F_{age} = \Theta_{age} \cdot (age - 40)$			
Otherwise $F_{age} = 0$			
If liver disease, then $F_{liver} = \Theta_{liver}$			
Otherwise $F_{liver} = 1$			
NONMEM estimates			
	Parameter estimate	SE	Interindividual variability(CV) (log normal)
Θ_{CL}	5.3 ml · kg^{-1} · min^{-1}	0.5	
Θ_{age}	0.036	0.018	
Θ_{liver}	0.68	0.08	
CL			+46%/−32%
V_1	0.42 L · kg^{-1}	0.017	+18%/−16%[b]
Q	660 ml · min^{-1}	78	+58%/−37%
V_{ss}	134 L	9.1	+89%/−48%
Residual intraindividual variability: ±19%			
−2 · log likelihood value: 4326			

[a]SE, standard error of estimates; CV, coefficient of variation; BW, body weight.
[b]Variability of V_1 nested within variability of V_{ss}.

bayesian regression to obtain individual estimates of pharmacokinetic parameters when an inadequate number of data point is available for each subject in order to perform an individual subject pharmacokinetic characterization.

Bayesian estimates are biased toward the average population parameter value, and therefore the correlation (if there is any) observed on the scatter plots between the bayesian estimates and the demographic factors will be less than what one would observe if the true individual pharmacokinetic parameters were known. However, the final goal of the population data analysis is to find the major demographic factors that explain interindividual variability in the data set. If the correlation is large enough to be seen in the scatter plots (Figs. 1, 2, and 3), it has a greater likelihood of being clinically relevant. Effects of small magnitude (e.g., a factor increasing clearance by 10%) are probably not clinically relevant when one considers that the remaining variability between individuals in the pharmacokinetic parameters is much higher (i.e., interpatient variability for clearance is ±38% in the present study).

The proposed graphical approach does not take into account correlation between demographic factors. Indeed, we found a large effect of the ASA physical status rating on clearance, with a decrease in clearance in individuals of poorer physical status, but the plots of ASA score versus age showed a high correlation between these two factors. This finding confirms the observed fact that older people tend to be less healthy than young individuals. NONMEM could not discriminate between the age effect and the ASA physical status effect on clearance. No regression convergence could be obtained when both effects were entered into the model at the same time. As a result, we left ASA rating out of the final model and age was chosen as the factor of prime importance, as previously shown by Greenblatt *et al.* (2).

The approach we present is a reasonable compromise between the time one is willing to invest in a population pharmacokinetic analysis and the size of the effects one is trying to detect. A demographic effect that is too small to be seen in a scatter graph is probably not relevant. An additional advantage of the proposed method is that the scatter graphs provide information on the shape of the relationship between pharmacokinetic parameter and demographic factor. The correct model for the effect of demographic factor (e.g., linear model vs. exponential model) can therefore be found more rapidly with NONMEM since we already have some information about its shape. The time saved by using the proposed method is considerable. The present midazolam analysis was completed in 3 weeks on a relatively slow machine (OPUS 100 PM 32-bit add-on "computer on a card" using AT&T UNIX as operating system and hosted in an IBM-AT clone), whereas the

traditional NONMEM approach would have taken months. Only 39 NONMEM runs were necessary to arrive at the final results shown in Table II; the traditional NONMEM approach would have required hundreds of runs.

Finally, we propose that programs for population pharmacokinetic analysis, such as NONMEM, should ideally provide a graphical method to examine the correlation of demographic factors with pharmacokinetic parameters directly, without one having to go through the bayesian regression step as had to be performed in the present work.

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A Pharmacokinetic Model Describing the Removal of Circulating Radiolabeled Antibody by Extracorporeal Immunoadsorption

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Extracorporeal immunoadsorption is a new technique for removal of circulating radiolabeled antibody from the peripheral blood (1) to reduce background activity for improved tumor imaging, and (2) to reduce whole-body and marrow toxicity when high doses of radiolabeled antibodies are used for antitumor therapy. A pharmacokinetic model was developed to describe plasma disappearance of ^{111}In-KC-4G3 prior to, during, and after immunoadsorption in humans. The model is developed based on a two-compartment open model, and during immunoadsorption a third compartment is added for removed radioactivity by the immunoadsorption column. Goodness-of-fit statistics indicate a good fit of the model to the data. The resulting pharmacokinetic parameters for a selected patient are $V_1 = 2.64$ L, $V_{2s} = 3.64$ L, $t_{1/2\alpha} = 3.77$ hr, and $t_{1/2\beta} = 48.5$ hr. The immunoadsorption clearance ($CL_{IA} = 19.3$ ml/min) was 21-fold greater than the patient's plasma clearance ($CL_{10} = 0.899$ ml/min), indicating a very effective immunoadsorption process. The model predicts an increase in plasma radioactivity upon termination of immunoadsorption, probably due to redistribution of radioactivity from the extravascular compartment to the plasma in response to the rapid decline in plasma radioactivity during immunoadsorption. Two series of simulations were performed to examine the influence of onset time and duration of immunoadsorption. In series one the onset time was varied and in series two immunoadsorption duration was varied. In series one, the predicted radioactivity amounts adsorbed by the immunoadsorption column ranged from 75% of the injected dose (4-hr onset) to 52% of the injected dose (24-hr onset). In series two, immunoadsorbed radioactivity ranged from 32% (2-hr duration) to 64% of the injected dose (12-hr duration). When instituted as early as 4 hr, the predictions suggest that

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